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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,544	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *34-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33 and 52-58* is/are rejected.

7)☒ Claim(s) *4,12,19,27 and 53-55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on February 5, 2007 is acknowledged. Claims 1-58 are currently pending. In the response, Applicant amended claim 52. Claims 34-51 are withdrawn from consideration as being drawn to a non-elected invention. It is noted that claims 34-51 have the status identifier "original". They should be listed as "withdrawn".

Applicant's arguments regarding the previously made rejections have been fully considered and were found persuasive, in part, as discussed in greater detail below. This Office Action contains new grounds of rejection not necessitated by amendment in sections 4, 6-9, 14, and 15, and therefore, is made non-final.

Sequence Listing

2. Applicant's submission of a Sequence Listing in paper and computer readable form on May 14, 2007 is acknowledged. The application is now in compliance with the Sequence Rules.

Claim Objections

3. Claims 4, 12, 19, and 27 are objected to because of the following informalities:

(a) Claim 4 appears to contain a typographical error in line 2, where "are" is recited in place of "is".

(b) Claim 12 appears to contain a typographical error in line 10, where "the a nucleic acid" is recited.

(c) Claim 19 appears to contain a typographical error in line 2, where "complement" is recited for "complementary".

(d) Claim 27 appears to contain a typographical error in line 2. It would appear that the word "to" was omitted after the word "corresponding".

Claims 53-55 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 53-55 are not further limiting, because they recite statements of intended use that do not further limit the claimed method.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 contains the trademark/trade name Master Amp ™ Amplitherm™ DNA polymerase. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade

name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a DNA polymerase, and accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-5, 8, 11, 26, 27, 32, and 53-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Kaufman et al. (US 6,383,754 B1; newly cited).

These claims are drawn to a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA comprising linker ligation and restriction enzyme digestion.

Regarding claim 1, Kaufman teaches a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA comprising (see Illustration 4 at columns 49-51):

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA (see column 49, line 40 - column 50, line 13, where fragment A is prepared)

(b) attaching at least one linker to the nucleic acid (column 50, lines 14-30)

(c) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of the mRNA (column 50, lines 32-50)

(d) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA (column 50, line 51 – column 51, line 50).

Regarding claims 2-4, the method taught by Kaufman inherently produces fragments that are about 5-100 bp, about 15-30 bp, and about 10-30 bp.

Regarding claim 5, Kaufman teaches that the nucleic acid in step (a) is an mRNA (column 49, lines 40-43 and column 7, lines 53-63).

Regarding claim 8, Kaufman teaches that the nucleic acid in step (a) is derived from a biological sample or a cDNA library (column 7, lines 53-63).

Regarding claim 11, Kaufman teaches that step (a) in the method of claim 1 comprises synthesizing first strand cDNA using RNA as a template and producing cDNA/RNA hybrids and recovering a nucleic acid corresponding to the 5' end region of the mRNA (see column 49, line 40 – column 50, line 13, where fragment A is prepared and recovered for subsequent adapter ligation and analysis).

Regarding claim 26, Kaufman teaches sequencing the DNA fragment prepared by the method of claim 1 (see column 51, lines 27-51, where the DNA fragments are sequenced by hybridization; see also, column 53, lines 4-13, where pyrosequencing is taught).

Regarding claim 27, Kaufman teaches that the method of claim 1 further comprises amplifying the nucleic acid corresponding to the 5' end region of the mRNA using a DNA polymerase (column 51, lines 9-18).

Regarding claim 32, Kaufman teaches that the method of claim 1 further comprises attaching the collected nucleic acid to beads (see, for example, Illustration 3 at columns 48-49).

Regarding claims 53-55, it is noted that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In this case, the method taught by Kaufman is inherently capable of being used for the development of research tools, diagnostic tools, a reagent, or a kit. Therefore, Kaufman anticipates the instant claims 53-55.

7. Claims 1-8, 11, 17, 19-21, 23-33, and 52-56 are rejected under 35 U.S.C. 102(e) as being anticipated by Pedersen (US 2003/0113737 A1; newly cited).

These claims are drawn to a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA comprising linker ligation and restriction enzyme digestion.

Regarding claim 1, 5-7, and 17, Pedersen teaches a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5’ end region of an mRNA comprising:

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA by substituting a 5' cap structure of the mRNA with an oligonucleotide that comprises a recognition site for a restriction enzyme that cleaves within the nucleic acid corresponding to the 5' end of the mRNA (see paragraphs 254, 256, and 257; see also Figure 12, steps I-III and the accompanying description in paragraph 61)

(b) synthesizing a first strand cDNA using the mRNA as a template (see paragraphs 254 and 256; see also Figure 12, step IV and the accompanying description in paragraph 61)

(c) synthesizing a second strand cDNA using the first strand cDNA as a template (see paragraphs 254 and 256; see also Figure 12, step V and the accompanying description in paragraph 61)

(d) cleaving a resulting double-stranded cDNA with the restriction enzyme (see paragraph 258)

(e) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA that comprises a linker moiety and part of the cDNA corresponding to the 5'end of the mRNA (see paragraphs 257-258).

Regarding claims 2-4, Pedersen teaches that the length of the DNA fragment recovered in step (e) is ranges from about 6 to more than 200 nucleotides (paragraph 194). Pedersen further teaches specific examples falling within this range, specifically DNA fragments of 8, 10, or 12 nucleotides (paragraph 194). Thus, the teachings of Pedersen anticipate the claimed ranges of about 5-100 bp, about 15-30 bp, and about 10-30 bp.

Regarding claims 8 and 56, Pedersen teaches that the nucleic acid in step (a) is an mRNA obtained from a biological sample (paragraph 209, for example).

Regarding claim 11, Pedersen teaches that step (a) in the method of claim 1 comprises synthesizing first strand cDNA using RNA as a template and producing cDNA/RNA hybrids (see Figure 12, steps I-IV and paragraphs 61, 254, and 256) followed by recovering a nucleic acid corresponding to the 5' end region of the mRNA (see paragraphs 256-257).

Regarding claim 19, Pedersen teaches that the second strand cDNA is synthesized using a primer that has the sequence of the linker (paragraph 61). These primers are inherently partially complementary to the linker region (i.e. they contain at least 2 consecutive nucleotides that are complementary to the linker region - see pages 30-33 for specific examples of such adapters).

Regarding claims 20, 21 and 32, Pedersen teaches that biotin is included in the linker and that the recovering step comprises binding the biotin moiety to bead-immobilized streptavidin (see paragraphs 252, 257-258, 262, and 791).

Regarding claims 23-25, Pedersen teaches that the restriction enzyme is a Class IIS restriction enzyme (see paragraphs 254 and 256-258), such as Bpm I (paragraphs 785 & 791) or BsgI (page 31).

Regarding claim 26, teaches Pedersen sequencing the DNA fragment prepared by the method of claim 1 (see, for example, paragraphs 33, 37, and 42).

Regarding claims 27-29, Pedersen teaches that the method of claim 1 further comprises amplifying the nucleic acid corresponding to the 5' end region of the mRNA

(paragraphs 30 and 524-533) using a heat-stable DNA polymerase, such as Taq DNA polymerase (paragraph 596).

Regarding claims 30 and 31, Pedersen teaches that, in the method of claim 1, the first strand cDNA is synthesized and fractionated by hybridization to a plurality of nucleic acids (paragraphs 257-260).

Regarding claim 33, Pedersen teaches concatamerizing the DNA fragments prepared by the method of claim 1 (paragraph 33, for example).

Regarding claim 52, Pedersen teaches that the method of claim 1 further comprises synthesizing the first strand of the nucleotide sequence by extending the 5' end region of the nucleotide sequence (see paragraphs 254, 256, and 257; see also Figure 12, steps I-IV and the accompanying description in paragraph 61).

Regarding claims 53-55, Pedersen teaches that the method of claim 1 can be used for the development of diagnostic tools (paragraphs 34-36, 43, and 737-745), research tools (paragraphs 34-42), or kits (paragraphs 36, 44, and 754-757). It is also noted that the limitations recited in the instant claims 53-55 are statements of intended use that do not further limit the claimed process steps. Since the methods taught by Petersen can inherently be used for the development of research tools, diagnostic tools, and kits, this reference anticipates claims 53-55.

8. Claims 1-5, 8, 11, 26-28, 30, 32, 33, and 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Kinzler et al. (US 5,695,937; cited previously).

These claims are drawn to a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA comprising linker ligation and restriction enzyme digestion.

Regarding claim 1, Kinzler teaches a method for preparing a fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprising:

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA (see column 4, lines 1-7 and Figure 1A, where cDNA is prepared from an mRNA template)

(b) attaching at least one linker to the nucleic acid (see Figure 1A and column 4, line 47 - column 5, line 50, where linkers are ligated to the 5' end after cleavage with the "anchoring enzyme")

(c) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of an mRNA (see Figure 1A and column 5, lines 45-60, where cleavage with the Type IIS "tagging enzyme" is taught)

(d) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA (see Figure 1A-1B and column 6, line 10 - column 7, line 67).

Kinzler expressly teaches application of the above method to the isolation of a fragment corresponding to the 5' end of an mRNA at column 4, lines 33-41, column 4, lines 47-50, and column 4, lines 65 - column 5, line 12.

Regarding claims 2-4, Kinzler teaches that the fragment is 6-30 base pairs, and preferably 9-11 base pairs (column 6, lines 14-16). Kinzler further teaches specific

examples of 9 base pair tags (see Table 1 in column 10). Therefore, Kinzler anticipates the claimed fragment length ranges of about 5-100 bp, about 15-30 bp, and about 10-30 base pairs.

Regarding claims 5 and 8, Kinzler teaches that the nucleic acid in step (a) is an mRNA derived from a biological sample (see column 4, lines 1-7 and column 9, lines 10-12).

Regarding claim 11, Kinzler teaches that step (a) in claim 1 above comprises:

(a1) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (column 4, lines 1-7)

(a2) recovering a nucleic acid that corresponds to the 5' end of the mRNA from the cDNA/RNA hybrids (column 4, line 47 – column 5, line 11).

Regarding claim 26, Kinzler teaches sequencing the DNA fragment produced by the method of claim 1 (column 7, lines 17-21 and lines 64-67).

Regarding claim 27, Kinzler teaches that the method of claim 1 further comprises amplifying the nucleic acid corresponding to the 5' end region of the mRNA by a DNA polymerase (column 6, lines 36-42).

Regarding claim 28, Kinzler teaches use of the T4 DNA polymerase (column 9, lines 29-30). The specification does not define the term "heat-stable", and since the T4 DNA polymerase is stable at 37°C, for example, this is a heat-stable polymerase.

Regarding claims 30 and 32, Kinzler teaches that the first strand cDNA (part of the double-stranded cDNA molecule generated by Kinzler in column 4, lines 1-7) is

fractionated by physical means (column 4, line 47 – column 5, line 12), which includes attaching the collected nucleic acid to beads (column 9, lines 16-18).

Regarding claim 33, Kinzler teaches preparing a concatemer comprising one or more DNA fragments by ligating one or more fragments obtained by the method of claim 1 (column 7, lines 6-21).

Regarding claims 53-55, Kinzler teaches that the method is applicable to development of diagnostic and research tools (column 13, line 16 – column 14, line 17) and also kits (column 8, lines 1-27). It is also noted that the limitations recited in the instant claims 53-55 are statements of intended use that do not further limit the claimed process steps. Since the methods taught by Kinzler can inherently be used for the development of research tools, diagnostic tools, and kits, this reference anticipates claims 53-55.

9. Claims 1-5, 8, 11, 26-32, and 53-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Fischer et al. (US 2004/0002104 A1; cited previously). This pre-grant publication obtains benefit of Provisional Application No. 60/375,782, filed April 26, 2002.

Regarding claim 1, Fischer teaches a method for preparing a fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprising:

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA (see paragraph 80)

(b) attaching at least one linker to the nucleic acid (see paragraphs 81, 84, and 86)

(c) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of an mRNA (see paragraph 87)

(d) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA (see paragraphs 92-93).

Regarding claims 2-4, Fischer teaches that examples of the Q adaptor that are 26 nt, 29 nt, and 27 nt (see SEQ ID Nos: 5, 8, and 12, respectively; see also paragraphs 87, 88, and 90). These adaptors contain an MmeI site or a BpmI recognition site at the 3'terminus. Since these enzymes cleave approximately 20 nucleotides from the recognition site, the resulting fragments described above are 46-49 nucleotides in length, which is about 5-100 bp, about 15-30 bp, and about 10-30 bp.

Regarding claims 5 and 8, Fischer teaches that the nucleic acid in step (a) is an mRNA derived from a biological sample (see paragraph 80).

Regarding claim 11, Fischer teaches that step (a) in claim 1 above comprises:

(a1) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (paragraph 80)

(a2) recovering a nucleic acid that corresponds to the 5' end of the mRNA (paragraphs 92-93).

Regarding claim 26, Fischer teaches sequencing the DNA fragment produced by the method of claim 1 (paragraphs 152 and 154).

Regarding claims 27-29, Fischer teaches that the method of claim 1 further comprises amplifying the nucleic acid corresponding to the 5' end region of the mRNA by a DNA polymerase, specifically the heat-stable Pfu polymerase (paragraphs 126 and 190-191).

Regarding claims 30-32, Fischer teaches that the first strand cDNA is synthesized and fractionated by physical means (paragraphs 80, 92, and 93), which includes attaching the collected nucleic acid to beads via hybridization to a plurality of nucleic acids (paragraphs 136-139).

Regarding claims 53-55, Fischer teaches that the method is applicable to development of diagnostic and research tools (paragraphs 44-47). It is also noted that the limitations recited in the instant claims 53-55 are statements of intended use that do not further limit the claimed process steps. Since the methods taught by Fischer can inherently be used for the development of research tools, diagnostic tools, and kits, this reference anticipates claims 53-55.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 6, 31, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited previously) in view of Maruyama et al. (Gene (1994) 138: 171-174; cited previously).

Kinzler teaches the method of claims 1-5, 8, 11, 26-28, 30, 32, 33, and 53-55, as discussed above.

Kinzler teaches that the 5' cap of the newly synthesized cDNA can be utilized for labeling or binding a capture means for isolation of a 5' defined nucleotide sequence tag (column 5, lines 7-11). However, Kinzler does not teach substitution of the 5' mRNA cap with an oligonucleotide.

Maruyama teaches a method (oligo capping) for isolating full-length cDNA transcripts comprising substitution of the 5' cap structure in the mRNA template with an oligonucleotide (see abstract and Figure 1). Maruyama teaches that the method is a rapid and simple way to isolate the 5' end of a cDNA transcript (see abstract and page 171, column 2 – page 172, column 1; see also page 174, column 1).

Regarding claims 6 and 52, Maruyama teaches: (a) substitution of the 5' cap in an mRNA template with an oligonucleotide and (b) synthesizing a first strand cDNA using

the mRNA as a template to produce a second nucleic acid corresponding to the 5' end of the mRNA (see Figure 1 and page 172).

Regarding claim 31, Maruyama teaches that the nucleic acid is fractionated by hybridization to a plurality of nucleic acids (the PCR step on page 172 utilizes a plurality of nucleic acid primers that hybridize to the target. Following amplification the products are fractionated in an agarose gel).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize oligo capping as taught by Maruyama in the method of Kinzler. As discussed above, one application of the method taught by Kinzler was to generate sequence tags from the 5' end region of a cDNA transcribed from an mRNA sample (column 4, lines 33-41 and column 5, lines 7-11). Since Maruyama taught that conventional reverse transcription protocols often generated a high percentage of truncated products (page 171) and further taught a rapid and simple method for selecting full-length transcripts (see abstract and page 172), an ordinary artisan would have been motivated to perform the oligo-capping procedure taught by Maruyama prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, and thereby improve the ability to generate 5' end-specific sequence tags using the method of Kinzler. This improved generation of 5' end-specific sequence tags would have improved the ability of the Kinzler method to identify novel sequences in the 5' region of an mRNA sample. Thus, the methods of claims 6, 31, and 52 are *prima facie* obvious over Kinzler in view of Maruyama.

12. Claims 9, 10, 12, 14-16, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited previously) in view of Carninci et al. (Genomics (1996) 37: 327-336; cited previously).

Kinzler teaches the method of claims 1-5, 8, 11, 26-28, 30, 32, 33, and 53-55, as discussed above.

Regarding claims 9, 10, 12, 14, and 15, Kinzler teaches that the 5' cap of the newly synthesized cDNA can be utilized for labeling or binding a capture means for isolation of a 5' defined nucleotide sequence tag (column 5, lines 7-11). However, Kinzler does not teach conjugation of a selective binding agent to the 5' cap of the mRNA.

Regarding claims 10, 14-16 and 58, Kinzler teaches that the cDNA may be labeled with selective binding substances such as biotin and digoxigenin for capture by the matching binding substances streptavidin and an anti-digoxigenin antibody, respectively (column 5, lines 7-11). Kinzler also teaches the use of magnetic streptavidin-coated beads for capture (column 9, lines 15-18).

Carninci teaches a high efficiency method ("CAP trapper") for isolating full-length cDNA molecules (see Figure 1 and pages 328-329).

Regarding claim 9, the method of Carninci comprises synthesizing first strand cDNAs using RNA as a template and producing cDNA/RNA hybrids of the resulting first-strand cDNAs and the RNAs (page 328, column 1 "First-strand cDNA preparation" and Figure 1), selecting a particular cDNA/RNA hybrid that has the 5' cap structure of the mRNA using a selective binding substance which specifically recognizes the 5' cap structure (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and

Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin beads), and recovering a nucleic acid corresponding to the 5' end of the mRNA (page 328, "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1).

Regarding claim 10, Carninci teaches preparation of a full-length cDNA using the method described above (see abstract and page 328, column 2). Carninci further teaches that the selective binding substance is attached to a support (page 328, column 2, where the selective binding substance is magnetic beads coated with streptavidin).

Regarding claim 12, the method of Carninci comprises:

(a) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (page 328, column 1 "First-strand cDNA preparation" and Figure 1)

(b) conjugating a selective binding substance to a 5' cap structure of an mRNA present in the RNAs, thereby extending the 5' (page 328, column 2, "Biotinylation of diol groups of RNA"; see also Figure 1)

(c) contacting the cDNA/RNA hybrids with a support, wherein another matching selective binding substance is fixed to the support, and the matching selective binding substance (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin-coated magnetic beads)

(d) recovering the a nucleic acid corresponding to the 5' end of the mRNA from the mRNA fixed to the support (page 328 "Blocking of magnetic beads and capturing the

nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin beads).

Regarding claims 14, 16, and 58, Carninci teaches that the selective binding substance is biotin and that the matching binding substance is streptavidin. Carninci further teaches that the streptavidin is coated on magnetic beads (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1).

Carninci teaches, "The overall efficiency and yield of the full-length cDNA is thus far superior to other conventional methods for the preparation of full-length cDNA libraries. Our method allows the preparation of high-content full-length cDNA libraries, even from relatively small quantities of tissues or early embryos, with no bias in representation since no PCR amplification step has been introduced (page 328, col. 1)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate the CAP trapper method taught by Carninci into the method of Kinzler. As discussed above, one application of the method taught by Kinzler was to generate sequence tags from the 5' end region of a cDNA transcribed from an mRNA sample (column 4, lines 33-41 and column 5, lines 7-11). Since Carninci taught that conventional reverse transcription protocols often generate a high percentage of truncated products (page 327) and further taught an extremely efficient, high-yield method for selecting full-length transcripts (see page 328 cited above), an ordinary artisan would have been motivated to attach a biotin molecule to the mRNA template as suggested by Carninici prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, and thereby improve the ability to

generate 5' end-specific sequence tags using the method of Kinzler. Increasing the number of full-length cDNA molecules in the pool prior to restriction enzyme digestion and generation of tags would have improved method taught by Kinzler by increasing its ability to identify novel sequences in the 5' region of an mRNA sample. Finally, since Kinzler expressly taught use of the 5' cap structure for capture of 5' end regions (see column 5, lines 7-11), an ordinary artisan would have expected a reasonable level of success in incorporating the CAP trapping procedure of Carninci into the method of Kinzler. Thus, the methods of claims 9, 10, 12, 14-16, and 58 are *prima facie* obvious over Kinzler in view of Carnici.

13. Claims 13 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited previously) in view of Carninci et al. (Genomics (1996) 37: 327-336; cited previously) and further in view of Edery et al. (Molecular and Cellular Biology (1995) 15(6): 3363-3371; cited previously) and further in view of Das et al. (Physiological Genomics (2001) 6: 57-80; cited previously).

The combined teachings of Kinzler and Carninci result in the method of claims 9, 10, 12, 14-16, and 58 as discussed above.

Neither Kinzler nor Carninci teaches that the selective binding substance is a cap-binding protein or a cap-binding antibody.

Edery teaches a method ("CAPture") of isolating full-length cDNA transcripts based on affinity capture using the cap-binding protein eIF-4e (see abstract). The method of Edery comprises the following steps: reverse transcription of mRNA to generate a cDNA/RNA hybrid, RNase A treatment, binding of eIF-4e to the 5' cap structure of the

mRNA to selectively bind full-length RNA/cDNA hybrids, and binding of the eIF-4e/RNA/cDNA complex to anti-eIF-4e conjugated to sepharose beads (see Methods section, page 3364, column 2 – page 365, column 1).

Das presents a review of methods for obtaining full-length cDNA molecules. Das compared affinity selection methods taught by Carninci (cap trapper) and Edery (affinity selection using the cap-binding protein eIF-4e) and reported that the Carninci method was not specific. Specifically, Das stated:

> [I]f we compare the ability of cap trapper to discriminate between cDNA duplex with capped mRNA (generated *in vitro*) or duplexed with uncapped mRNA (generated *in vitro*), then we are unable to obtain specific selection of capped over uncapped transcripts (J. Pelletier, data not shown). This is likely due to the fact that biotin-hydrazide can also react with unoxidized RNA due to incipient reaction of cytosine residues. Hence, addition of biotin is not solely directed toward the cap structure. Also, it is important to note that the oxidation reaction with $NaIO_4$ is difficult to control, and the molar ratio of periodate to substrate is important, otherwise one gets destruction of base rings (page 73).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the affinity selection method of Edery for the cap trapper method taught by Carninci in the method resulting from the combined teachings of Kinzler and Carninci. As discussed above, Edery taught a method for isolating full-length cDNA molecules comprising affinity purification using the cap-binding protein eIF-4e (see above). An ordinary artisan would have been motivated to substitute the affinity selection method of Edery for the cap trapper method of Carnici, since Das taught that the affinity selection method was more specific and did not involve the use of the potentially RNA-degrading reagent $NaIO_4$ (see above). Thus, the methods of claims 13 and 57 are *prima facie* obvious over Kinzler in view of Carnici and further in view of Edery and further in view of Das.

14. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen (US 2003/0113737 A1; newly cited) in view of Shibata et al. (Biotechniques (2001) 30(6): 1250-1254; cited on an IDS).

Pedersen teaches the method of claims 1-8, 11, 17, 19-21, 23-33, and 52-56, as discussed above.

Pedersen does not teach that the first strand cDNA is ligated to a double-stranded linker, which is then used to prime second strand cDNA synthesis, as required by claim 18.

Shibata teaches a method for cloning full-length cDNA via linker ligation termed the single strand linker ligation method (SSLLM) (see abstract). Regarding claim 18, the method of Shibata comprises the following steps: (a) reverse transcription of an mRNA template and isolation of the resulting first strand cDNA, (b) ligation of a partially double-stranded linker to the first-strand cDNA, (c) synthesis of second strand cDNA using the linker ligated in step (b), (d) digestion of the resulting double-stranded cDNA, (e) cloning of the digested cDNA molecule (see Figure 1 and pages 1250, 1251, and 1253). Shibata teaches that the above method is especially suitable for full-length cDNA cloning and further states, "Finally, the SSLLM might be used as universal ss-DNA priming method [e.g., in cloning 5'ends of genes by using rapid amplification of cDNA ends (RACE)], replacing RNA ligase (with DNA substrates) and homopolymer tailing (page 1253, column 2)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Shibata to the method taught by Pedersen. An ordinary artisan would have been motivated to synthesize second strand cDNA molecules

using a partially double-stranded linker ligated to first strand cDNA molecules, since Shibata taught that this method was especially suitable for synthesizing and cloning full-length cDNA molecules (page 1253). An ordinary artisan also would have recognized that using a ligated linker to prime second strand cDNA synthesis would reduce undesirable internal priming, and therefore, would have been motivated to incorporate the SSLL method of Shibata into the method of Pedersen. An ordinary artisan would have had a reasonable expectation of success in doing so, since Shibata expressly taught that the method was suitable for full-length cDNA cloning and universal priming of second strand cDNA synthesis (page 1253). Thus, the method of claim 18 is *prima facie* obvious over Pedersen in view of Shibata.

15. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen (US 2003/0113737 A1; newly cited) in view of Cocuzza et al. (US 5,484,701; newly cited).

Pedersen teaches the method of claims 1-8, 11, 17, 19-21, 23-33, and 52-56, as discussed above.

Pedersen teaches that the linker contains biotin to permit streptavidin-mediated capture rather than digoxigenin to permit capture with an anti-digoxigenin antibody.

Cocuzza teaches a method for isolating primer extension products prior to electrophoresis comprising biotinylation of the primer extension product and isolation with a support-immobilized avidin (see abstract and column 3, line 55 – column 4, line 20). Regarding claim 22, Cocuzza teaches that biotinylated primer extension products may also be isolated using an antibody-antigen capture system, wherein the antigen

digoxigenin is attached to the primer and the primer extension products are captured with a support-immobilized anti-digoxigenin antibody (column 7, lines 28-43). In this passage, Cocuzza further teaches that this system performs as well as the biotin-avidin system, and that methods for immobilizing antibodies on solid supports are known.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the biotin-streptavidin capture method taught by Pedersen with the digoxigenin-anti-digoxigenin antibody capture method taught by Cocuzza. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Cocuzza taught that digoxigenin-mediated capture was an art-recognized equivalent of the biotin-avidin capture method taught by Pedersen (column 7, lines 28-43). As noted in MPEP 2144.06, substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious. Thus, the method of claim 22 is *prima facie* obvious over Pedersen in view of Coccuza.

Response to Arguments

16. Applicant's arguments, see pages 17-18, filed February 5, 2007, with respect to the objections to the specification, have been fully considered and are persuasive. Applicant's amendment and submission of a Sequence Listing overcomes the objections, and therefore, they have been withdrawn.

Applicant's arguments, see pages 18-19, filed February 5, 2007, with respect to the rejection of claim 52 under 35 U.S.C. 112, 2nd paragraph, have been fully considered and are persuasive. Applicant's amendment overcomes the rejection, and therefore, it has been withdrawn.

Applicant's arguments, filed February 5, 2007, regarding the rejection of claims 1-5, 8, 11, 26-28, 30, 32, 33, and 52-55 under 35 U.S.C. 102(b) as being anticipated by Kinzler, have been fully considered but were not found persuasive. In view of the amendment to claim 52, this rejection currently applies to claims 1-5, 8, 11, 26-28, 30, 32, 33, and 53-55.

Applicant argues that the Kinzler reference does not teach all of the elements of claim 1. More specifically, Applicant argues that the SAGE method taught by Kinzler does not teach a method that permits the identification and collection of DNA fragments that correspond to the actual 5' end of an mRNA molecule (see pages 19-20). Applicant argues that the cleavage with the tagging enzyme taught by Kinzler in Figure 1 does not produce a fragment corresponding to the 5' end of the mRNA molecule since the 5' terminal region remains attached to the bead (page 19). Applicant also argues that Kinzler teaches internal cleavage of the cDNA sequences using a restriction enzyme, and therefore, the method does not permit collection and identification of DNA fragments corresponding to the actual 5' end of the molecule (page 20). Applicant further argues that the Kinzler reference teaches the use of a tag sequence that is fixed and defined for each RNA molecule and notes that a fixed internal tag sequence necessarily prevents determination and capture of the 5' end corresponding to an mRNA molecule (page 20).

Applicant's arguments were not found persuasive, because the claims are drawn to a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA. The broadest reasonable interpretation of "a 5' end region" is not limited to the 5' terminus, and therefore, the disclosure of Kinzler, where a region derived from the 5' end of an mRNA transcript is analyzed, meets the claimed limitation.

It is further noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Applicant's arguments, filed February 5, 2007, regarding the rejection of claims 1, 2, 5-12, 14, 16-21, 23-32, 52-56, and 58 under 35 U.S.C. 102(e) as being anticipated by Fisher have been fully considered and were found persuasive, in part. Applicant argues that Provisional Application 60/375,782, filed on April 26, 2002 does not provide adequate support for the disclosure appearing in the cited pre-grant publication, and therefore, the Fischer reference has an effective filing date of April 26, 2003, which is later than the filing date of the instant application (June 12, 2002). Applicant's arguments were found persuasive with respect to claims 6, 7, 9, 10, 12, 14, 16-21, 23-25, 52, 56, and 58, and therefore these rejections have been withdrawn. However, Applicant's arguments were not found persuasive with respect to claims 1-5, 8, 11, 26, 27-32, and 53-55, because the '782 application provides adequate support at pages 12-20 for the disclosure present in the pre-grant publication. Therefore, the rejection of claims 1-5, 8, 11, 26-32, and 53-55 under 35 U.S.C. 102(e) as being anticipated by Fischer has been maintained.

Applicant's arguments, filed February 5, 2007, regarding the rejection of claims 6, 9, and 31 under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Maruyama have been fully considered, but they were not found persuasive. This rejection is currently applicable to claims 6, 31, and 52. Applicant argues that Kinzler does not teach all of the elements of independent claim 1, and the teachings of Maruyama do not cure the deficiencies of the Kinzler reference (see page 22). This argument was

not found persuasive, because as discussed above, Kinzler teaches all of the elements of claim 1. Therefore, the Maruyama reference is only relied upon for its teachings relevant to dependent claims 6, 31, and 52.

Also, in response to applicant's argument that there is no suggestion to combine the Kinzler and Maruyama references (see page 22), the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine the teachings of Maruyama and Kinzler is clearly set forth in the above rejection. Since Maruyama taught that the production of truncated cDNA molecules was a problem inherent in conventional reverse transcription methods and further taught a solution to this problem (oligo-capping), an ordinary artisan would have been motivated to incorporate oligo-capping into the method taught by Kinzler in order to improve the generation of full-length cDNA transcripts for SAGE analysis. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Applicant's arguments, filed February 5, 2007, regarding the rejection of claims 9, 10, 12, 14-16, and 58 under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Carnici, have been fully considered, but they were not found persuasive. Applicant argues that Kinzler does not does not teach all of the elements of independent claim 1, and the teachings of Carnici do not cure the deficiencies of the Kinzler reference

(see page 23). This argument was not found persuasive, because as discussed above, Kinzler teaches all of the elements of claim 1. Therefore, the Carnici reference is only relied upon for its teachings relevant to dependent claims 9, 10, 12, 14-16, and 58. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Applicant's arguments, filed February 5, 2007, regarding the rejection of claims 13 and 57 under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Carnici and further in view of Ederly and futher in view of Das, have been fully considered, but they were not found persuasive. Applicant argues that Kinzler does not does not teach all of the elements of independent claim 1, and the teachings of the secondary references (Carnici, Ederly, and Das) do not cure the deficiencies of the Kinzler reference (see pages 23-24). This argument was not found persuasive, because as discussed above, Kinzler teaches all of the elements of claim 1. Therefore, the secondary references are only relied upon for their teachings relevant to dependent claims 13 and 57. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Conclusion

17. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amb

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